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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,274	RAMAKRISHNAN ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-78* is/are pending in the application.

4a) Of the above claim(s) *64-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/25/06;7/27/05;* 6/28/05; 12/1/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group I, claims 51-63, without traverse in the reply on 12 May 2006 is acknowledged. Applicants' further election of SEQ ID NO: 1 and SEQ ID NO: 7 with traverse is also acknowledged.

The traversal is on the grounds SEQ ID NOs: 25 and 28 are not patentably distinct because they are the full length heavy chain sequences (of antibodies M200 and F200) and therefore include the complete variable region of SEQ ID NO:1. Applicants argue that similarly, SEQ ID NO: 26 is the full length light chain sequence of M200 which includes the complete variable region of SEQ ID NO: 7. Since any search related to Group I, SEQ ID NOs: 1 and 7 should necessarily include the results for Group I, SEQ ID NOs: 25, 26, and 28 there is no search burden. Applicants requested that the restriction of the sequences be withdrawn.

Applicants' arguments are found persuasive.

2. Claims 51-78 are pending.

Claims 64-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim.

Claims 51-63 are examined on the merits.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 14, line 20, page 15, line 26, and page 44, line 10.

4. The disclosure is objected to because the Brief Description of the Drawings for Figure 2 on page 8 lists SEQ ID NOs: 1-12. However, Figure 2 itself does not list SEQ ID NOs: 1-12 but rather V_H and V_L 1-5 respectively. It is not clear which sequences in Figure 2 correspond to SEQ ID NOs: 1-12.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 51-58 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 recites the limitation "the constant region" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claims 51 and 55 are vague and indefinite. It is unclear from the claims (specifically, the semicolon on line 4) whether both the heavy chain variable region and the light chain variable region are required for the chimeric or humanized anti-alpha5beta1 antibody.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 51-58, and 63, are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus. " (See MPEP 2164).

In the instant case, the claims are drawn to an isolated antibody that specifically binds to an alpha5beta1 integrin protein wherein the light chain polypeptide comprises amino acid sequences having at least 95% identity to SEQ ID NOs: 7, 18, 22, 26, and 32 and the heavy chain polypeptide comprises amino acid sequences having at least 95% identity to SEQ ID NOs: 1, 16, 20, 25, 28, and 31. While the specification has provided sequence information for the antibody light and heavy chains that are 100% identical to the SEQ ID NOs above, the specification does not indicate which regions need to be conserved within the peptide sequence and which positions can tolerate mutations or differences for antibodies that are at least 95% sequence identical. Since the heavy and light chains of antibodies contain complementary determining regions (CDRs) which are crucial for antibody binding to the target antigen and can be affected by even a single individual amino acid substitutions, Applicants need to provide examples of sequences that are 95% identical which still retain binding capabilities to alpha5beta1 integrin.

Therefore, Applicants are not in possession of a genus of antibodies that have heavy chains and light chains that are at least 95% identical to SEQ ID NOs: 1, 16, 20, 25, 28, and 31 as well as 7, 18, 22, 26, and 32, respectively.

Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description

requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, 1st Written Description Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column). In the instant case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently,

Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

9. Claims 51-63 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling two chimeric antibodies HuM200-G4 and HuM200-g2m3 which contain heavy and light chains of SEQ ID NOs: 31 and 32, respectively, that bind to alpha5beta1 integrin, does not reasonably provide enablement for chimeric or humanized antibodies that have heavy and light chains with at least 95% sequence identity to SEQ ID NOs: 1, 16, 20, 25, 28, and 31, as well as 7, 18, 22, 26, and 32, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of

experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims and the nature of the invention: The claims are drawn to a chimeric or humanized antibody that binds alpha5beta1 integrin. The claimed antibodies comprise a heavy chain variable region comprising an amino acid sequence that is 95% identical to a sequence selected from the group of SEQ ID NO: 1, 16, 20, 25, 28, and 31. The antibodies also comprise a light chain variable region comprising an amino acid sequence that is 95% identical to a sequence selected form the group of SEQ ID NOs: 7, 18, 22, 26, and 32. Therefore, the claims encompass antibodies that include amino acid sequences substitutions and variations in the complementary determining regions (CDRs).

The state of the prior art and the level of predictability in the art: It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order

to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79:1979-1983, 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

The amount of direction provided by the inventor and the existence of working examples: The instant specification contains examples of only two humanized or chimeric antibodies that bind to alpha5beta1 integrin, see page 55, last paragraph, and figure 26. These antibodies, HuM200-G4 and HuM200-g2m3 have a heavy chain sequence corresponding to SEQ ID NO: 31 and a light chain sequence of SEQ ID NO: 32. There are no examples of humanized or chimeric antibodies which are 95% sequence identical to any of the SEQ ID NOs *and* bind to alpha5beta1 integrin in the specification.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed inventions without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC).

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that it is unlikely that humanized or chimeric

antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Double patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 51, and 54-63, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/830,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to chimeric antibodies that bind alpha5beta1 integrin. In addition, the claimed chimeric antibodies of both applications are composed of heavy and light chain regions composed of identical amino acid sequences (SEQ ID NOs: 1, 7, 16, 18, 20, 22, 25, 26, 28, 31, and 32).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 51, and 54-63, are directed to an invention not patentably distinct from claims 1-8 of commonly assigned 10/830,956. See the provisional obvious type double patenting rejection above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/830,956, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly

assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David Humphrey, Ph.D.

July 24, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER